Remarks

The above Amendments and these Remarks are in reply to the Office Action mailed January 15, 2007. Where appropriate, this Reply addresses points raised by the Examiner using the same numbering as in the Office Action.

An Information Disclosure Statement accompanies this REPLY, along with the appropriate fee.

3. Claims 57 and 59

Applicants herein withdraw Claims 57 and 59 without prejudice. Applicants note that the Office Action mailed July 5, 2005 stated: "[a]pplicant is required in reply to this action, to elect a single species to which the claims shall be restricted if no generic claim is finally held to be allowable." Office Action mailed July 5, 2005, page 4, second paragraph. Thus, Applicants believe that upon allowance of a generic claim, withdrawn claims are to be rejoined into this application. Additionally, Applicants reserve the right to prosecute withdrawn and other claims in continuing or divisional applications.

4-5. Rejections Under 35 U.S.C. §112

Claim 56 stands rejected under 35 U.S.C. §112, first paragraph for lack of enablement and for lack of written description for "an analog thereof, a functionally equivalent ligand, or a functionally equivalent endogenous ligand."

Applicants have removed these limitations from Claim 56, and now believe that this rejection is overcome.

Applicants have amended certain claims to specify "secondary neuroprotective agents." With the explicit disclosure of such specific agents, Applicants submit that the claims meet the enablement requirement.

6. Hypoxia and Ischemia are Disclosed in the Specification

Claims 30-35, 49-51 and 56-58 stand rejected under 35 U.S.C. §112, first paragraph for failing to meet the written description requirement for lack of support for treating "hypoxia or ischemia."

Applicants point out to the Examiner the specification as filed at least at pages 13-14, as follows: "Briefly, the rats were anaesthetised and maintained on a 2% halothane/oxygen mixture and the **right carotid artery ligated** ... They were then exposed to 15 minute **hypoxia** (8% oxygen in nitrogen)." Page 13 line 34 to page 14 line 2; emphasis added.

Applicants respectfully submit that the above support demonstrates written description of the full scope of the pending claims.

7. Rejections Under 35 U.S.C. §102

a. Inherent Anticipation

Claims 30, 32-33 and 58 stand rejected under 35 U.S.C. §102(b) as "being anticipated by Golab et al. ("Golab") in light of Burman and/or Nyberg..." Office Action, page 4. The rationale is that peripheral administration of GH putatively had some benefit (Golab) and that peripherally administered GH could pass through the blood-brain barrier (Burman and Nyberg), thus providing an "anticipation by inherency" rationale.

Applicants have amended Claim 30 to include the limitation that GH is administered "centrally to the brain of the patient via lumbar, intracerebroventricular (ICV) intraventricular, intraparenchyma or olfactory neural routes." By this, Applicants mean a direct administration of the GH to the brain and not via passage of GH from the periphery (i.e., systemic circulation) through the blood-brain barrier.

Applicants submit that such "central" administration is different from peripheral administration disclosed by Golab/Burman/Nyberg in that with "central" administration "to the brain," there is a substantially lower likelihood of deleterious side effects of GH (i.e., diabetogenic and/or lactogenic effects), side effects commonly found in patients treated with GH. Support for side effects of peripherally administered GH is found at least in the Appendix to this REPLY. The Appendix to this REPLY contains photocopies of portions of Goodman & Gilman's "The Pharmacological Basis of Therapeutics," Ninth Edition (1996)(hereinafter "Goodman"), which is a well-known textbook of pharmacology. Effects of GH are due to both direct effects and to indirect effects.

Direct Effects of GH

GH can exert direct effects on peripheral target tissues.

> Direct effects include the stimulation of the production of IGFs in the liver and other tissues, stimulation of triglyceride hydrolysis in adipose tissue, and the stimulatin of hepatic glucose output. These effects are potentiated by glucocorticoids and oppose the effects of insulin (and IGFs) on fat and carbohydrate metabolism (Davidson, 1987). Goodman, page 1366, third paragraph.

Indirect Effects of GH

In addition to direct effects noted above, other, indirect effects of GH are mediated via somatomedins, including IGF-1 and IGF-2. "In most tissues, growth hormone acts, indirectly through IGF-1, by increasing cell number rather than cell size. ... most organs and tissues respond to the hormone with an increase in size." Goodman, page 1366, right column, third full paragraph. "Although many tissues can synthesize IGF-1 and IGF-2, **the liver is considered to be the major source of circulating IGF-1** (Figure 55-1)." Page 1366, right column first full paragraph; emphasis added. "Indirect effects [i.e., mediated by IGF-1 or IGF-2] of growth hormone are insulin-like (Davidson, 1987) and, in contrast to the direct effects (see above) are inhibitied by glucocorticoids." Id. at paragraph 3.

> In general, administration of the hormone for several hours leads to metabolic effects that are opposite to those of insulin: increased hepatic glucose output, decreased glucose utilization, and increased lipolysis. **Growth hormone also induces insulin resistance** by blocking the actions of receptor-bound insulin. Thus, the net results of the metabolic actions fo growth hormone is to shift the source of fuel from carbohydrates to fats. These effects explain why **excessive amounts of growth hormone may lead to a diabetic state**. Page 1366 bridging to 1367; emphasis added.

Thus, an undesirable side effect of peripheral administration of GH is insulin resistance and a diabetes-like condition. These adverse effects can be decreased by administration of GH "centrally to the brain" as in Applicants claims. A difference in routes of administration is demonstrated by the finding that IGF-1 levels in the CSF were not increased by central administration of GH.

> Furthermore and as the applicants have found that growth hormone **administered centrally to the brain** is neuroprotective **without effecting** a concurrent increase in **IGF-1** levels. Specification, page 2, lines 9-11; emphasis added.

Additionally,

> Growth hormone **administered centrally** is effective as a neuronal rescue agent. The neuronal rescue effect occurred without a concurrent increase in CSF-IGF-1, demonstrating the neuroprotective effect is **independent of IGF-1**." Specification, page 17, lines 30-33; emphasis added.

Applicants submit that the lack of IGF-1 response is indicative of the difference in route of administration and is not intended to implicate merely a mechanism of action of GH. Further, the lack of an IGF-1 response is unexpected based on the well-known mechanism of GH action via somatomedins (e.g., IGF-1). This point is relevant to the rejection under 35 U.S.C. §103 below.

b. Golab is Not Enabled

In addition to Applicant's position that "centrally to the brain of the patient via lumbar, intracerebroventricular (ICV) intraventricular, intraparenchyma or olfactory neural routes" is not inherently anticipated by the peripheral administration disclosed by the combination of Golab, Burman and Nyberg, Applicants also submit that the evidence presented in Golab is so lacking in basic scientific validity as to be mere speculation.

First, according to the incomplete translation made available by the Examiner, Golab injected somatotropin (GH) intramuscularly. Unfortunately, the conclusion that somatotropin was responsible for the effects is put into serious question because other agents were also administered along with GH.

"We have applied somatotropin in 10 patients having cerebral apoplexies **in parallel with the other methods of therapy**." Page 5 of the translation, last paragraph; emphasis added. Unfortunately, these "other methods of therapy" were not disclosed. In one of the case studies (Case #2), Golab indicated that somatotropin was adjunctive. "The patient received the agents which compact the endothelium of vessels, specifically Calcium gluconicum, Vitamin P [sic], Vitamin C, and also the injections of somatotropin." Golab, page 8, third full paragraph.

These "other methods of therapy" were described in Golab as follows:

> [S]pecifically, use of the medical agents which are **compacting the epithelium** of vessels or **reducing the arterial blood pressure**, and also the **anti-thrombosis drugs** and those contributing to the improvement of blood circulation. Golab, page 3 first paragraph; emphasis added.

Thus, there were no controls to show that the therapeutic effect was due, in fact, to somatotropin . Therapeutic benefit could have been due to: (1) compacting the epithelium, (2) reducing arterial blood pressure, (3) an antithrombogenic effect, or (4) simply the passage of time.

Applicants submit that Golab could at best only speculate that somatotropin was the agent responsible for the observed effects of such multiple treatments. Although this speculation may have basis in some of the then-known effects of somatotropin (e.g, protein metabolism, tissue formation and the like, see Golab, page 3), Applicants submit that the level of speculation was so high as to render any proper scientific conclusion about somatotropin's neuroprotective effects suspect.

The Examiner concluded: "Golab teaches a method of administering the **same substance** in the **same manner** to treat the **same condition** as the instant invention. If Golab does not anticipate the claims, then the instant invention must logically not be enabled!" [Exclamation in original.]

Although 1 of the above conditions is met (i.e., somatotropin is GH), Applicants do not agree that the other 2 criteria are met. Although both Golab and Applicants treat cerebral hypoxia/ischemia), as stated above Applicants submit that Golab does reasonably enable therapeutic effects due to somatotropin administration because no proper controls were used. Further, the third condition (i.e., "same manner") is not met. As pointed out above, Applicants submit that there are substantial and therapeutically important differences in "the manner" of administration of GH. Simply, Golab's "intramuscular injection" is not the same as Applicants' administration of GH "centrally to the brain..." Thus, Applicants respectfully submit that the facts do not support the Examiner's rationale for anticipation.

8. Double Patenting

Claims 30-33, 49-50 and 58 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of U.S. patent No: 6,187,906 (the "906 patent") in view of Golab.

Applicants respectfully disagree that the combination of the '906 patent and Golab renders the instant claims obvious.

a. Standard for Obviousness Type Double Patenting (ODP)

According to the MPEP:

> Where the **claims** of an application are not the "same" as **those** of a first patent, but the grant of a patent with the claims in the application would unjustly extend the **rights granted by the first patent**, a double patenting rejection under nonstatutory grounds is proper. MPEP §804; emphasis added.

> A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting **claims** are not identical, but at least one examined application **claim** is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). MPEP §804II(B); emphasis added.

> In determining whether a nonstatutory basis exists for a double patenting rejection, the first question to be asked is - does any **claim** in the application define an invention that is anticipated by or is merely an obvious variation of an invention **claimed** in the patent? MPEP Id.; emphasis added.

Applicants respectfully submit that the above standards indicate that any double patenting rejection of the obviousness-type must be based on a comparison of the claim in the application and the claim(s) of

the prior patent. Thus, according to the MPEP, this type of ODP depends on the claims. Although the specification can be used to inform one of the meaning of the terms in a claim, it is the claim of the patent and the claim of the application that must not be patentably distinct to support an ODP rejection.

The factual inquiries for analyzing an ODP rejection are informed by Graham v. John Deere, 383 US1 (1966) and are:

A. Determine the scope and content of a patent claim relative to a claim in the application at issue;

B. Determine the differences between the scope and content of the patent claim as determined in (A) and the claim in the application at issue;

C. Determine the level of ordinary skill in the pertinent art; and

D. Evaluate any objective indicia of nonobviousness. MPEP §804II(B)(1).

Scope and Content of Claims of the '906 Patent

As pointed out by the Examiner, the the claims of the '906 patent are drawn to uses of the tripeptide, gly-pro-glu (GPE) to protect dopaminergic neurons from degeneration due to Parkinson's disease.

The Scope of the Instant Claims is Different from Those of the '906 Patent

The instant claims are drawn to uses of GH as a neuroprotective agent to treat hypoxia/ischemia. Applicants appreciate the Examiner's admission that the '906 patent claims do not teach methods of using GH as a neuroprotective agent.

Administering GH Centrally to the Brain Produces Unexpected Results

As pointed out above, administering GH "centrally to the brain" unexpectedly did not raise CSF IGF-1 levels. This finding is completely unexpected given the well-known property of GH to act via somatomedins (e.g., IGF-1).

b. Application of the Graham Factors: The Claims are Patentably Distinct

Applicants respectfully submit that each of the above factors tip the balance in favor of patentability over the claims of the '906 patent in view of Golub. First, GPE is not an obvious variant of GH. GPE is a tripeptide, whereas it is well known that GH is a protein having a molecular weight of about 22 kDaltons and about 191 amino acids, depending upon the source.

Next, GH is not an obvious variant of GPE for reasons stated above.

The only possible link between the '906 patent claims and the instant claims is the Golub reference. However, as pointed out above, Applicants's method of administering GH "centrally to the brain of the patient via lumbar, intracerebroventricular (ICV) intraventricular, intraparenchyma or olfactory neural routes" is neither taught no suggested by Golab (even in combination with Burman and/or Nyberg). The unexpected results obtained (i.e., finding no increase in CSF IGF-1 levels) means that even if combined, the prior art would not produce the invention as currently claimed.

Finally, although the Examiner stated: "[s]pecifically, the patent claims teach methods using GPE as a neuroprotective agent," (Office Action, page 8), the instant application does not claim GPE by itself as a neuroprotective agent. Claim 50 is directed to use of GPE as a secondary neuroprotective agent to be used along with GH. Thus, claim 50 of the instant application does not represent an unfair "extension of the rights to exclude" of the '906 patent. Applicants therefore respectfully request the examiner to withdraw the ODP rejection.

9. Interference

The Examiner noted that the Office normally will not institute an interference between applications or a patent and an application of common ownership." Office Action, page 7. Applicants appreciate this statement of policy. Applicants respectfully submit that the claims of the '906 patent and the instant claims are not interfering. Although GPE is claimed in the instant application, it is only within the context of adjunctive therapy **along with GH.** In the '906 application, no growth hormone is claimed.

10. Obviousness

Claims 30-33, 49-50, 56 and 58 stand rejected under 35 U.S.C. §103 as obvious over Golab in view of Gluckman ('906 patent). Applicants herein incorporate the comments herein relating to Golab.

a. Neither the '906 Patent Nor Golab Teaches Central Administration of GH

As noted, Golab teaches intramuscular administration of GH and not "central" administration "to the brain." Thus, if one were to combine Golab and the teachings of the '906 patent together, one would arrive at a peripheral administration of GH (taught by Golab) and not the "central" administration as claimed. As pointed out above, Applicants found unexpected results with administering GH "centrally to the brain," namely an absence of the expected increase in CSF IGF-1. Further, Golab neither taught nor suggested avoiding deleterious side effects of peripheral administration of GH by administering GH "centrally to the brain."

The teachings of the '906 patent do not make up for the lack of such teaching by Golab. Applicants submit that the '906 patent teaches that GPE can be neuroprotective and have play a therapeutic role in diseases of the central and the peripheral nervous system. However, Applicants submit that the '906 patent provides no expectation that administration of GH would be neuroprotective.

b. Golab is Not Enabled

Further, as noted above, Applicants submit that Golab does not fairly teach or suggest a neuroprotective role of GH. The therapeutic benefits reported in Golab may have been due to the "other methods" Golab used. Applicants submit that at best, Golab might provide an "invitation to experiment" to see if GH might be a neuroprotective agent. This standard "obvious to try" has been rejected by the courts and is not the proper standard of obviousness. Thus, Golab cannot provide a grounds for obviousness of the instant claims. Rather, Applicants submit that the instant rejection is based on impermissible hindsight reconstruction based on Applicants' own disclosure. Such hindsight reconstruction has been rejected by the courts and is not the proper standard of obviousness.

c. The Combination of "906 and Golab Does Not Render Applicant's Claims Obvious

Finally, the '906 patent discloses the use of a completely different compound, GPE, as a neuroprotective agent. Applicants have amended all of the independent claims to eliminate the phrase "an analog thereof" and similar language rejected under 35 U.S.C. §112.

The Examiner has not provided a "reasoned statement" supporting the idea that successful use of GPE as a neuroprotective agent as in the '906 patent, would be viewed by one of ordinary skill in the art as teaching that GH would also be neuroprotective when administered "centrally to the brain" without undue experimentation with a reasonable likelihood of success.

Even if the '906 patent were viewed as teaching administering GPE "centrally to the brain," such teaching does not carry over to a reasonable expectation that administration of GH "centrally to the brain..." would be neuroprotective as claimed. GPE and GH are very different peptides. GPE is a tripeptide; GH is a much larger peptide (191 amino acids). GPE has the same sequence as the N-terminal tripeptide of IGF-1. However, the Applicants' finding that GH administered "centrally to the brain" did not elevate IGF-1 indicates that there could be no increase in GPE in the CSF to account for the observed neuroprotective effects of GH. Thus, Applicants discovered that GH has novel and important neuroprotective effects that can be useful for treating hypoxia and ischemia in human beings.

12. The Finality of This Rejection is Improper

Applicants respectfully submit that the current Final rejection is improper and should be withdrawn.

According to the MPEP, "[a] second or any subsequent action on the merits in any application or patent involved in reexamination proceedings should **not be made final** if it includes a rejection, on **prior not of record** ..." MPEP §706.07(a); emphasis added. Applicants respectfully submit that Golab is not properly of record because no complete translation is available.

Applicants respectfully point out that consideration of any piece of prior art must be analyzed "as a whole." Without a complete translation, Applicants have not had an opportunity to evaluate the disclosures, teachings and suggestions independently.

In the prior Office Action, no translation of Golab was provided. The only basis for the rejections over Golab were based on the Examiner's informal interpretation of the reference. The Examiner indicated that a translation would be provided with a subsequent Office Action (i.e., this Office Action). . Applicants thank the Examiner's willingness to provide a complete translation of Golab, and await its receipt.

However, with this Office Action, only a partial translation of Golab was provided. Applicants have not yet had the opportunity to respond to Golab "as a whole." Below the portion of Golab that was translated, the following comment was provided by the translator.

"[Incomplete - several pages are not available for translation]"

Applicant notes that the missing pages are from the Discussion section, and also requests the Examiner to take Official Notice that Discussion sections of published academic papers may be highly relevant to interpretation of the data presented and to any conclusions drawn, including for example, **caveats, disclaimers and indications of poorly understood phenomena**. Such teachings by the authors of Golab may be highly relevant to evaluation of the reasonableness of the conclusions drawn by the author as well as the Examiner.

Additionally, there was no explanation in this Office Action of why the prior Reply "necessitated a new ground for rejection." Applicants believe that the Final Rejection in this Office Action represents an impermissible violation of Applicant's due process under regular Office practice or any statutory or Constitutional scheme. A statutory deadline was provided for filing a Reply, even though Applicants have not been presented with the primary reference being applied against the claims. On one hand, Applicants are being given a deadline for Reply, with financial penalties or even abandonment of the application at risk, and on the other hand, do not have the means to fully evaluate and respond to the rejections. Applicants

believe that this "catch 22" situation was contemplated by neither Congress in enacting 35 U.S.C. nor the Office in preparing either 37 C.F.R. or the MPEP.

Applicants specifically reject any suggestion that the prior Reply constituted or this Reply constitutes a waiver of Applicant's rights to completely evaluate the conclusions of the Examiner.

Therefore, Applicants respectfully request the Examiner to withdraw the finality of the instant Office Action in the interests of Office Procedure and basic fairness to the Applicants, to provide a complete translation of Golab and to provide another Examination and Reply, if necessary, as a matter of right.

Applicants herewith provide an Information Disclosure Statement. Applicants request examination of the pending claims in light of the disclosed references.

Conclusion

In light of the above, Applicants respectfully request the following: (1) the Examiner tenter this amendment , (2) the Examiner to consider that all claims are in condition for allowance, and (3) to provide a Notice of Allowance. In the event that the Examiner believes that the claims are not in condition for allowance, Applicants request the Examiner to withdraw the finality of this rejection and to provide another Office Action and permit another Reply as a matter of right. Finally, the Examiner is respectfully requested to telephone the undersigned if he can assist in any way in expediting issuance of a patent.

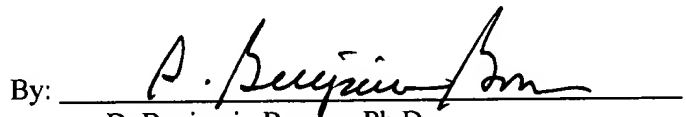
This Reply is timely filed and no PETITION FOR EXTENSION OF TIME is required.

Please note the change of Attorney Docket Number. The new docket number is NRNZ-01006US0.

The Commissioner is authorized to charge any underpayment or credit any overpayment to Deposit Account No. 50-4089 for any matter in connection with this response, including any fee for extension of time, which may be required.

Respectfully submitted,

Date: March 26, 2007

By: 

D. Benjamin Borson, Ph.D.
Reg. No. 42,349

CUSTOMER NO. 66936
BORSON LAW GROUP, PC
1320 WILLOW PASS ROAD, SUITE 490
CONCORD, CALIFORNIA 94520-5232
Tel: (925) 395-2060